REMARKS

Introductory Comments:

Claims 1-8, 11-17 and 20-27 were examined in the Office Action dated 20 July 2001. Applicant notes with appreciation that the following rejections have been withdrawn: **(a)** the rejection of claims 1-5, 7, 8 and 11-14 under 35 U.S.C. §112, first paragraph; **(b)** the rejection of claim 6 under 35 U.S.C. §112, first paragraph; **(c)** the rejection of claims 1-8, 11-17 and 20-27 under 35 U.S.C. §112, second paragraph; **(d)** the rejection of claims 1-4, 7, 8, 11-17, 20-23 and 25-27 under U.S.C. §102(b); and **(e)** the rejection of claims 1, 5, 7, 8 and 12 under 35 U.S.C. §102(b).

However, the following claim rejections were maintained: **(1)** claims 1, 12-14 and 24-27 remain rejected under 35 U.S.C. §102(a) as unpatentable over A-Mohammadi et al. (1998) *Gene Therapy* 5:76-84 ("Mohammadi"); and **(2)** claims 1, 12-14 and 24-27 remain rejected under 35 U.S.C. §102(b) as unpatentable over Hofmann et al. (1996) *Proc. Natl. Acad. Sci.* 93:5185-5190 ("Hofmann").

In addition, the following new claim rejections have been entered: **(1)** claims 1-4, 6-8, 11-17 and 20-23 are rejected under 35 U.S.C. §112, first paragraph, as nonenabled; **(2)** claims 1, 5, 6, 13-15, and 21-22 are rejected under 35 U.S.C. §112, second paragraph, as indefinite; **(3)** claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25 are rejected under 35 U.S.C. §102(e) as unpatentable over U.S. Patent No. 6,194,389 to Johnston et al. ("Johnston"); **(4)** claims 24-27 are rejected under 35 U.S.C. §102(e) as unpatentable over U.S. Patent No. 6,200,751 to Gu et al. ("Gu"); **(5)** claims 1, 13-15, and 21-22 are rejected under 35 U.S.C. §103(a) as unpatentable over Johnston in view of Mohammadi or Hofmann; and **(6)** claims 1 and 5 are rejected under 35 U.S.C. §103(a) as unpatentable over Laube et al. (1994) *Human Gene Therapy* 5:853-862 ("Laube") in view of Mohammadi or Hofmann.

All standing rejections are respectfully traversed for the reasons discussed herein below.

Overview of the Amendments:

Applicant, by way of this Amendment, has provided minor amendments to claims 5 and 6. More particularly, claim 5 has been amended to remove language objected to by the Office, and claim 6 has been amended to correct its dependency from claim 1 to claim 5. Support for these amendments can be found throughout the specification and in the claims as originally filed. Accordingly, no new matter has been added by way of these claim amendments, and the entry thereof is respectfully requested.

Election of Claims:

In the Action dated 20 July 2001, the Office indicated that applicant had "confirmed the election of [the Group I claims] without traverse." Office Action at page 2. Applicant notes that this statement is incorrect, since applicant had traversed the restriction requirement (see Applicant's Response dated 4 April 2001, pages 3-5). Since the Office has neither confirmed that the Group I claims encompass both types of particle delivery techniques, nor entered a new restriction requirement that includes a new group drawn to the second type of particle delivery, applicant hereby requests that the Office either respond to the traversal or provide a new restriction requirement in a new non-final Office Action.

The Rejection under 35 U.S.C. §112, first paragraph:

Claims 1-4, 6-8, 11-17 and 20-23 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. This is a new ground of rejection. In particular, the Office acknowledges that applicant's specification is "enabling for an *in vitro* method of obtaining expression in mammalian cells of an antigen of interest ... and the same method *in vivo* for non-humans, wherein said nucleic acid construct is delivered by intramuscular, intravenous, intradermal injection or transdermal particle delivery; and coated particles suitable for use in particle-mediated nucleic acid immunisation [and] a particle acceleration device being loaded with the same

coated particles." Office Action at page 6. However, the Office asserts that the specification "does not reasonably provide enablement for other embodiments of the claims."

The Office has supported it's assertion by arguing as follows: **(a)** with regard to the *in vivo* method, "when read in light of the specification the sole purpose for such a method is to induce a protective immune response in a host" (Office Action at page 7); **(b)** "it is highly unlikely that the naked nucleic acid construct could be effectively transferred into mammalian cells via inhalation, oral or mucosal routes of delivery to express the encoded antigen at an effective amount to elicit the desired host immune responses ... because said nucleic acid construct could be subjected to degradation prior to being transferred to the appropriate cells for expression" (Office Action at page 8); **(c)** "it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention [since] McCluskie noted that the route of administration of plasmid DNA vaccines influences the strength and nature of immune response in mice and non-human primates, and that optimal dose and immunization schedule most likely vary between species, [and] Lietner stated that 'although genetic vaccines have been significantly improved, they may not be sufficiently immunogeneic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials'" (Office Action at pages 8-9, bridging paragraph); and **(d)** "the breadth of the instant claims encompasses a functional variant of a minimal promoter sequence ... there is a high degree of unpredictability associated with ... this claimed embodiment (citing Rudinger as stating] 'the significance of particular amino acids sequences for other aspects of biological activity can not be predicted *a priori*' [and citing Ngo et al.. as support for] this unpredictability is further underscored by the fact that the relationship between the sequence of a peptide and its tertiary structure is not well understood and is not predictable" (Office Action at pages 9-10, bridging paragraph). Applicant respectfully traverses each of these assertions for the following reasons.

(a) The Office has asserted that, with regard to the recited *in vivo* methods, "when read in light of the specification the sole purpose for such a method is to induce a protective immune response in a host" (Office Action at page 7). The Office then concludes that applicant's specification is not sufficiently enabling for this embodiment. Applicant respectfully disagrees. First of all, it is unclear how the Office has arrived at its conclusion that applicant's specification teaches that **the sole purpose** of applicant's recited *in vivo* methods is to induce a **protective immune response**. Applicant cannot find any support whatsoever for this position. Applicant submits that his specification makes it clear that the recited methods can be used to elicit any type of desired immune response including, for example, the methods can be used in the context of a therapeutic vaccine. Since a "therapeutic vaccine" is a composition that is administered to an already infected or afflicted subject, such vaccines cannot by definition be used for the sole purpose of providing a protective immune response. In fact, applicant is uncertain as to just what the Office is asserting here. For example, is it the Office's position that any immune response that is not a protective immune response is simply not useful and therefore would not be contemplated by the skilled artisan? Applicant would strongly disagree with such a position. Applicant's *in vivo* methods can be used for many purposes other than to induce a protective immune response, and all of these methods are both useful and enabled by the specification. Applicant requests that, should the Office wish to maintain the rejection on this basis, it provide clarification of just how it has arrived at it's conclusion that only protective immune responses are contemplated by a reading of applicant's specification. Otherwise, reconsideration and withdrawal of this basis of rejection is respectfully requested.

(b) The Office has asserted that "it is highly unlikely that the naked nucleic acid construct could be effectively transferred into mammalian cells via inhalation, oral or mucosal routes of delivery to express the encoded antigen at an effective amount to elicit the desired host immune responses ... because said nucleic acid construct could be subjected to degradation prior to being transferred to the

appropriate cells for expression" (Office Action at page 8). The Office then concludes that applicant's specification is not sufficiently enabling. Applicant respectfully disagrees. Initially, applicant notes that the Examiner seems to be relying upon personal knowledge of inhaled, oral and mucosal administration of naked nucleic acid constructs since no reference has been cited in support of this blanket assertion. In addition, applicant is personally aware of numerous examples of inhalation and mucosal delivery of nucleic acid constructs, seemingly flying in the face of the Office's assertion that "it is highly unlikely" that nucleic acids can be delivered in these ways. Accordingly, applicant hereby requests that, if the Examiner is indeed in possession of certain facts within their own personal knowledge that relate to anticipated or expected difficulties in administering nucleic acids by inhalation, oral or mucosal routes, the Examiner identify specific subject matter from suitably citable references by way of an affidavit pursuant to 37 C.F.R. §1.104(d)(2). After such a showing has been officially made of record, applicant will have a fair chance to contradict or otherwise traverse the Office's position. Without such a showing, the bald, non-supported assertion is not properly citable against the claims. In the absence of such a showing, the present ground of rejection must be withdrawn.

(c) The Office has asserted that "it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention [since] McCluskie noted that the route of administration of plasmid DNA vaccines influences the strength and nature of immune response in mice and non-human primates, and that optimal dose and immunization schedule most likely vary between species, [and] Lietner stated that 'although genetic vaccines have been significantly improved, they may not be sufficiently immunogeneic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials'" (Office Action at pages 8-9, bridging paragraph). The Office then concludes that applicant's specification is not sufficiently enabling. Applicant respectfully disagrees. With regard to the Office's reliance on McCluskie

that "**optimal** dose and immunization schedule most likely vary between species," applicant submits that this has no bearing whatsoever on the scope of enablement provided by applicant's specification. Applicant is unaware of any requirement under Section 112 that requires him to provide teaching of **optimization** of his recited methods.

Applicant submits that he has provided an enabling disclosure commensurate with the scope of the claimed invention. In particular, applicant has provided, in great detail, descriptions of the construction of minimal promoter constructs that express antigen sequences in suitable host cells and methods for administering such constructs into suitable host cells *in vivo*. Applicant has exemplified his invention using standard, art-recognized animal modeling systems. The claimed methods have been shown effective in such art-recognized systems in bringing about extremely robust immune responses. Applicant's claims are drawn to these very methods.

Accordingly, applicant has provided a disclosure which teaches the manner and process of making and using the invention in terms which correspond to the scope of the claims. This disclosure must, therefore, be taken as in compliance with the enablement requirement of Section 112, unless there is reason to doubt the objective truth thereof. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). In this regard, the Office bears the initial burden under Section 112 of challenging applicant's presumptively correct disclosure, which burden can only be met by a showing of sufficient evidence that one of skill in the art would doubt the veracity of the disclosure. Applicant respectfully submits that the Office has not met this burden by arguing that "optimal doses and immunization schedules vary between species." It is well settled that an *in vitro* or *in vivo* animal model example in a specification constitutes a "working model" if that example "correlates" with a disclosed or claimed method. If a particular model is recognized as correlating to a specific condition, then it must be accepted by the Office absent express evidence otherwise. Even if such evidence is tendered, it must be weighed against the evidence for correlation and

decided whether one of ordinary skill in the art would accept the model as reasonably correlating. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Here again, the mere argument that dose or vaccine schedule "optimization" may vary from species to species falls far short of establishing that applicant's art-recognized animal model experiments fail to enable the recited methods in other species.

With regard to the Office's reliance on Leitner et al. (2000) *Vaccine* 18:765-777 ("Leitner") to support the instant ground of rejection, specifically Leitner's statement that "although genetic vaccines have been significantly improved, they may not be sufficiently immunogeneic for **therapeutic** vaccination of patients with infectious disease or cancer in clinical trials," applicant notes that this statement seems to have been read out of context. The Leitner reference is directed to a discussion of **therapeutic** DNA and RNA-based vaccines. See the abstract. Thus, when the entire document is actually read, it is immediately clear that Leitner merely states that some existing vaccine compositions may not be suitable for a specific type of vaccination, that is therapeutic vaccines. For example, a vaccine that provides a substantially humoral (antibody) immune response may not be entirely suitable for therapeutic vaccination, and a vaccine that provides a substantially TH-2 dominated cellular immune response may likewise not be suitable in a therapeutic vaccine context. However, the skilled artisan understands that even if these vaccines are not useful in therapeutic vaccines, they would still be entirely useful to provide, for example, prophylactic protection or for use in vaccination against an autoimmune disease or allergy disorder. The Office's apparent assertion that this statement by Leitner establishes that applicant's recited methods are unpredictable is simply unsupported by the record. What has happened is that the Office has read a single sentence from the abstract out of context with the rest of the article, and has concluded something completely incorrect. This is improper and the instant ground of rejection must be withdrawn.

(d) The Office has asserted that "the breadth of the instant claims encompasses a functional variant of a minimal promoter sequence [and] there is a

high degree of unpredictability associated with ... this claimed embodiment (citing Rudinger as stating] 'the significance of particular amino acids sequences for other aspects of biological activity can not be predicted *a priori*' [and citing Ngo et al.. as support for] this unpredictability is further underscored by the fact that the relationship between the sequence of a peptide and its tertiary structure is not well understood and is not predictable" (Office Action at pages 9-10, bridging paragraph). The Office then concludes that applicant's specification is not sufficiently enabling. Applicant respectfully disagrees.

In particular, applicant wishes to remind the Office that an enhancer is an untranslated nucleic acid sequence. (A promoter is a segment of nucleic acid sequence to which a polymerase attaches, thereby aligning the polymerase so that transcription will initiate at a specific site in an operatively connected site.) What the Office has cited in support of it's assertion that applicant's functional variant minimal promoters are not enabled are two references (J.A. Parsons (1976) "Peptide Hormones" University Park Press, and Ngo et al. (1994) in "The protein folding problem and tertiary structure prediction," K. Merz et al. eds., Birkhauser, pp. 491-495) that relate to changes made to protein sequences (i.e., changes to sequences that **are translated** to provide a functional translation product--**protein**). Contrary to the Office's assertion that "similar unpredictability also occurs in the relationship between the nucleotide sequence of a minimal promoter and its promoting activity," these cited references have no connection whatsoever to the issue of the functionality of variant promoter sequences. Reconsideration and withdrawal of the instant ground of rejection is thus respectfully requested.

For all of the foregoing reasons, then, applicant submits that the rejection of claims 1-4, 6-8, 11-17 and 20-23 under 35 U.S.C. § 112, first paragraph, is improper and simply not supported by the record. Reconsideration and withdrawal is thus earnestly solicited.

The Rejections under 35 U.S.C. §112, second paragraph:

Claims 1, 5-6, 13-15 and 21-22 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. This is a new ground of rejection. Initially, the Office has objected that in claims 5 and 6, the phrase "the cells are reintroduced into the subject" is unclear on the basis that "there is no nexus between this step and the expression of the antigen of interest in mammalian cells [as recited in the preamble of claim 1]." Office Action at page 12. The Office has suggested that applicant use an independent claim to recite such *ex vivo* methods.

In response, applicant draws the Office's attention to claims 5 and 6 as amended herein. Applicant submits that these amended claims avoid the Office's objections, and the reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §112, second paragraph, is respectfully requested.

The Office has also objected that claims 13, 14, 21 and 22 are unclear on the basis of the term "a functional variant." The Office goes on "although the term is vaguely defined in the instant specification [pages 10-11], it is still not clearly defined because it may vary from a native promoter sequence and may encompass functional fragments of a native promoter sequence." The Office then concludes that the metes and bounds of the claims can not be clearly determined. Applicant respectfully traverses for the following reasons.

The primary purpose of Section 112's requirement for clarity and precision is to ensure that the public is informed of the metes and bounds of the claimed invention. Applicant also notes that definiteness of claim language must be analyzed, not in a vacuum, but in light of: **(1)** the content of the disclosure provided by the specification; **(2)** the teachings of the prior art; and **(3)** the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

As already discussed in the Amendment dated 4 April 2001, the term "minimal promoter" intends only those promoter sequences that have been stripped and separated from their native enhancer sequences. As stated at page 11, lines 3-8, the ability of a variant sequence to act as a "minimal promoter" (as expressly

defined) and "thus retain function can be determined by routine experimentation. Applicant's specification goes on to suggest that the variant sequence be coupled to a reporter gene in a suitable expression system and the presence or absence fo expression thus readily determined. Applicant submits that such experimentation is readily within the ambit of the routineer.

The definiteness of applicant's term "functional variants" must be assessed in light of his broad disclosure, the teachings of the prior art, and the sort of interpretation that one of ordinary skill in the art would give, and the tools available to those skilled in the art. Applicant submits that when the term "functional variants" is assessed in light of the express definitions provided by the specification, the suggested assays to assess functional variants, and the general skill in the art, it is clear that the claims meet the requirements of Section 112, second paragraph. Accordingly, reconsideration and withdrawal of the rejection of claims 13, 14, 21 and 22 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Finally, the Office has objected that claims 14 and 22 for inclusion of the limitation "the hCMV immediate early promoter" on the basis that "there is insufficient antecedent basis for this limitation in the claim or in the base claims [13 and 21]." Applicant respectfully disagrees. Applicant's recitation of "the" hCMV IE promoter is a clear and concise recitation of a specific sequence and is just as proper as, for example, a claim that recites "the sequence of SEQ ID No X." There is no proper issue regarding antecedence with respect to this term. Reconsideration and withdrawal of the rejection of claims 14 and 22 under 35 U.S.C. §112, second paragraph, is thus earnestly solicited.

The Rejections under 35 U.S.C. §102:

Claims 1, 12-14 and 24-27 remain rejected under 35 U.S.C. §102(a) as anticipated by Mohammadi. In particular, the Office asserts that Mohammadi describes "an enhancerless positive feedback regulatory vector construct pSaiIV transcribing both the tetracycline-controlled transactivator (tTA) and mGM-CSF

from a modified tTA-responsive bidirectional promoter." Applicant respectfully traverses the rejection.

All of the rejected claims require the transfer into a mammalian cell of a nucleic acid construct comprising a minimal promoter sequence linked to a coding sequence for an **antigen** of interest. Mohammadi thus clearly fails to anticipate applicant's claims since there is no disclosure of a minimal promoter linked to an antigen-encoding sequence. It is well established that, to be anticipatory under Section 102, a cited reference must disclose within its four corners each and every element of the claimed invention.

The Office has attempted to overcome this basic flaw by arguing that **if** the Mohammadi construct was delivered to an individual **in vivo AND** the individual did not normally harbor such a gene product, then an immune response would be generated. In other words, the Office suggests that it is sufficient under Section 102 to argue that one could ignore the actual reading of a cited document and somehow convert strictly *in vitro* experimentation to an *in vivo* method (not even so much as contemplated by Mohammadi), purposely apply this method to an individual that does not harbor native transactivator or mouse GM-CSF, and engender an immune response. In other words, the Office has had to completely re-write the entire Mohammadi reference to now teach completely unintended uses, where those uses have been moved from cell culture to a living animal and in fact applied to an inappropriate animal to get an immune response. This is of course improper. Applicant reminds the Office that it must stay within the four corners of the cited reference and not draft it's own "anticipatory" art by making fantastic, sweeping and totally inappropriate changes to a prior art document

Applicant's claims require that the coding sequence be an antigen sequence. Mohammadi simply fails to anticipate administration of an antigen sequence driven by a minimal promoter that is expressed in a host cell. It does not matter what the Office believes could have been described in Mohammadi if the authors had instead intended something entirely different. All that matters is what

Mohammadi actually states, which is an *in vitro* method for expressing native genes of interest in a mouse cell. Accordingly, Mohammadi fails to disclose applicant's recited methods, and it cannot anticipate claims 1 and 12-14. Reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(a) is thus earnestly solicited.

Claims 1, 12-14 and 24-27 remain rejected under 35 U.S.C. 102(b) as anticipated by Hofmann. The Office asserts that Hofmann describes "a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence fused to the human CMV immediate early minimal promoter." The Office thus concludes that the claims are anticipated by the reference. Applicant respectfully traverses.

Here again, applicant draws the Office's attention to claims 1 and 12-14, all of which require the transfer into a mammalian cell of a nucleic acid construct comprising a minimal promoter sequence linked to a coding sequence for an **antigen** of interest. In be anticipatory under Section 102, a cited reference must disclose within its four corners each and every element of the claimed invention. Hofmann clearly does not disclose applicant's recited methods within its four corners.

Once again, the Office has attempted to overcome this basic flaw by arguing that **if** the Hofmann construct was delivered to an individual **in vivo AND** the individual did not normally harbor such a gene product, then an immune response would be generated. In other words, the Office argues that it is somehow present or inherent in Hofmann to convert strictly *in vitro* experimentation to an *in vivo* method (not even so much as contemplated by Hofmann), purposely apply this method to an individual that does not harbor native β-Gal, and engender an immune response. In other words, the Office has had to completely re-write the entire Hofmann reference to now teach completely unintended uses, where those uses have been moved from cell culture to a living animal and in fact applied to an inappropriate animal to get an immune response. This is of course improper.

Applicant reminds the Office that it must stay within the four corners of the cited reference and not draft it's own "anticipatory" art by making fantastic, sweeping and totally inappropriate changes to a prior art document

Applicant's claims require that the coding sequence be an antigen sequence. Hofmann simply fails to anticipate administration of an antigen sequence driven by a minimal promoter that is expressed in a host cell. It does not matter what the Office believes could have been described in Hofmann if the authors had instead intended something entirely different. All that matters for the purposes of consideration under Section 102 is what Hofmann actually states, which is an *in vitro* method for β-Gal. Accordingly, Hofmann fails to disclose applicant's recited methods, and it cannot anticipate claims 1 and 12-14. Reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(a) is thus earnestly solicited.

Claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25 stand rejected under 35 U.S.C. §102(e) as unpatentable over Johnston. This is a new ground of rejection. In particular, the Office asserts that Johnston somehow discloses applicant's recited minimal promoters. To support this assertion, the Office has directed applicant's attention to Johnston's abstract and the specification at columns 5 and 6. (Office Action at pages 14-15.) Applicant respectfully traverses for the following reasons.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)). Finally, in order to anticipate, a prior art

reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986).

All of applicant's claims include the express limitation that a minimal promoter sequence is used to drive expression of the attached antigen sequence. The term "minimal promoter" is clearly and unambiguously defined in the specification as only encompassing those promoters where the native enhancer sequence has been excised or otherwise removed. Accordingly, in order for Johnston to anticipate, the promoters described therein must have had a native enhancer sequence excised or otherwise removed. Johnston clearly fails to teach such promoters. There is nothing whatsoever within the four corners of Johnston that even comes close to describing applicant's minimal promoters. Since Johnston clearly fails to describe truncation or excision of enhancer sequences from the promoter systems described therein (excision of native enhancers from human alpha-actin promoter, human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, retrovirus long terminal repeats (e.g., the RSV long terminal repeat), and the metallothionin gene promoter, Johnston column 5, lines 45-55 and working examples), the Office must be proceeding under a theory of inherency to provide the missing limitation. In other words, the Office seems to assert that a native enhancer *may* have been excised from one of Johnston's disclosed promoter systems since enhancers are listed as optional regulatory elements.

However, the Office's rejection also fails even under a theory of inherency. The fact that a certain characteristic *may* have occurred in the prior art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert,* 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). In fact, to establish inherency, the evidence must make clear that the missing descriptive matter (in this case, the excision of native enhancer sequences form the Johnston promoters) is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons

of ordinary skill in the art. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). It is beyond argument that the Office cannot establish that Johnston's promoters *necessarily* had native enhancer sequences excised from them, nor is possible for the Office to argue that those skilled in the art would have understood this to have been the case.

Johnston therefore cannot possibly anticipate any of applicant's claims, since each and every element of applicant's claims are **NOT** inherent in, **NOR** disclosed expressly by the anticipating reference and there is **NO** identity between applicant's recited methods and reagents and the promoters described by Johnston. IN addition, since Johnston is absolutely silent with respect to excising or otherwise removing a native enhancer from a promoter sequence, it cannot be enabling for applicant's recited minimal promoters since, in order to anticipate, a prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. Reconsideration and withdrawal of the rejection of claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25 under 35 U.S.C. §102(e) is thus earnestly solicited.

Claims 24-27 stand rejected under 35 U.S.C. §102(e) as anticipated by Gu. In particular, the Office asserts that Gu "disclosed the isolation and use of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a protein of interest." The Office supports this position with the assertion that "the promoter including a region resulting in selective expression in endothelial cells, between -1 and -220 based on the positions relative to the ATG [of EPCR, col 1, lines 58-63; col 4, lines 24-36] meets the limitation of 'minimal promoter' of the instant invention which merely requires a promoter sequence without its endogenous enhancer." (Office Action at pages 15-16, bridging paragraph.) Applicant respectfully traverses for the following reasons.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988).

Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411 (Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)).

All of applicant's claims include the express limitation that a minimal promoter sequence is used to drive expression of the attached antigen sequence. The term "minimal promoter" is clearly and unambiguously defined in the specification as only encompassing those promoters **not** having a native enhancer sequence. Accordingly, in order for Gu to anticipate, the promoters described therein must not have a native enhancer sequence. Gu clearly fails to teach such promoters.

More particularly, the Office has defined Gu's "minimal promoter" (-220 to -1) as falling under the scope of applicant's minimal promoters. However, a more careful read of Gu reveals that the (-220 to -1) promoter region contains a "transcription control elements required for constitutive expression in endothelial cells (specifically, the region of the promoter from -220 to -177), see Gu at column 2, lines 48-53. Gu refers to this as a minimal promoter since it does not also include the large vessel-specific control element (between -1080 and -700); the thrombin induction element (between -345 and -337) and the serum response element (between -350 and -280). See Gu, column 1, lines 63-67; column 2, lines 4-6; column 2, lines 55-62; and column 3, line 64 through column 4, line 14.

Gu therefore cannot possibly anticipate any of applicant's claims, since each and every element of applicant's claims are not inherent in nor disclosed expressly by the anticipating reference and there is no identity between applicant's recited methods and reagents and the promoters described by Gu. Reconsideration

and withdrawal of the rejection of claims 24-27 under 35 U.S.C. §102(e) is thus earnestly solicited.

The Rejections under 35 U.S.C. §103(a):

Claims 1, 13-15 and 21-22 were rejected under 35 U.S.C. §103(a) as unpatentable over the combination Johnston in view of Mohammadi or Hofmann. More particularly, the Office asserts that the primary reference to Johnston "teaches that the regulatory sequences ... are generally promoters which are operable in the target tissue cells, and that other regulatory elements which **may optionally** be incorporated intothe polynucleic acid sequence include **enhancers**" (Office Action at page 18, emphasis in original). The Office acknowledges that "Johnston does not specifically teach a minimal promoter having the limitations recited in the claims" (Office Action at page 19), but seeks to overcome this failure by arguing that the promoters used by Mohammadi and Hoffman "fall within the scope of a functional variant" (Office Action at page 20), and then concludes "it would have been obvious to an ordinarily skilled artisan to use the truncated minimal promoters disclosed by Mohammadi or Hofmann as the regulatory sequence ... in the polynucleic acid sequence [of] Johnston." Office Action at page 20. The Office asserts that the motivation to make this combination is provided by Mohammadi's "suggestion that the enhancerless positive feedback regulatory vector offers an efficient gene regulation which is suitable for most applications especially gene therapy." Office Action at pages 20-21, bridging paragraph. Applicant respectfully disagrees.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the

combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its asserted combination.

As already discussed herein above in regard to the Section 102 rejections, the Johnston reference fails to teach or disclose applicant's recited minimal promoters, much less the concept of providing minimal promoters. The Office has acknowledged this much in the discussion of the preset rejection (see Office Action at page 19). Accordingly, to establish *prima facie* obviousness, the Office must establish that there was the requisite motivation to modify and combine the references as it has asserted in its combination, that there was a reasonable expectation of success for the Office's proposed modification/combination; and that the prior art references taught or suggested all the claim limitations. Applicant submits that the Office has fallen far short of this basic burden, and has thus failed to establish *prima facie* obviousness over it's proposed combination of Johnston, Mohammadi and Hofmann.

More particularly, the Office has asserted that the requisite motivation to use the truncated minimal promoters disclosed by Mohammadi or Hofmann as the regulatory sequence in the polynucleic acid sequence of Johnston is provided by Mohammadi's "suggestion that the enhancerless positive feedback regulatory vector offers an efficient gene regulation which is suitable for most applications especially gene therapy," or that Hofmann "suggested that their autoregulatory cassette ... allows rapid delivery of inducible genes." Office Action at pages 20-21. Such an argument fails on the basis of the underlying scientific issued. Applicant asks why would Johnston, or for that matter any skilled artisan seeking to carry out a nucleic acid immunization, even consider a tetracycline-regulated promoter system (Mohammadi) or an inducible promoter (Hofmann)? The skilled artisan (prior to

reading applicant's enabling disclosure) would have just one thing in mind, that is, to use the most highly efficient and over-expressing promoter system available in order to overcome perceived issues with low-level expression, or low delivery efficiency. This is why applicant's recited invention is so nonobvious. Instead of maximizing the level of expression by ensuring that all native enhancers are available to increase promoter efficiency, applicant has taken the counter-intuitive approach to reduce the expression frequency from the promoter by removing the native enhancer sequence. As disclosed in applicant's examples, removal of the enhancer sequence reduced expression levels form the minimal promoter constructs, but in all cases these low expression systems resulted in dramatic increases in the immune response. This is a surprising and unexpected result, and certainly not one that was obvious to the skilled artisan. There is no proper scientific basis for the Office's assertion that the skilled artisan would have been motivated to use a promoter that required a coadministered product (the tetracycline antibiotic of Mohammadi) in order to regulate expression of a vaccine sequence, nor is there any plausible basis for the Office's assertion that the skilled artisan would have been motivated to use an inducible promoter system such as Hofmann's. In fact, use of these systems in the Johnston methods would have rendered those methods unsatisfactory for their intended purpose.

It is thus absolutely unsupportable for the Office to assert that it was obvious to have modified Johnston using Mohammadi and/or Hofmann in order to arrive at applicant's recited invention. This is because it is well established that if a proposed modification would render the prior art being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

For these reasons, then, the rejection of claims 1, 13-15 and 21-22 under 35 U.S.C. §103(a) is improper. The Office's proposed modification necessitates that the clear teaching of the primary reference as well as the common understanding in

the art be ignored and that the modification render it unsatisfactory for its intended purpose. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 1 and 5 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Laube in view of Mohammadi or Hofmann. In particular, the Office asserts that Laube describes *"ex vivo* transduction of autologous non-human primate rhesus monkey fibroblasts .. with a retroviral vector encoding HIV-1 IIIB ENV/REV proteins." However, the Office acknowledges that "Laube do not teach specifically the use of a minimal promoter for expressing the antigen of interest." Office Action at page 21.

The Office seeks to overcome this failure by arguing that secondary references to Mohammadi and Hoffman provides the missing features, and that the motivation to make this combination is provided by Mohammadi's "suggestion that the enhancerless positive feedback regulatory vector offers an efficient gene regulation which is suitable for most applications especially gene therapy." Office Action at page 22. Applicant respectfully disagrees.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its asserted combination.

As discussed herein above, there is no proper scientific basis for the Office's assertion that the skilled artisan would have been motivated to use a promoter that required a coadministered product (the tetracycline antibiotic of Mohammadi) in order to regulate expression of a vaccine sequence, nor is there any plausible basis for the Office's assertion that the skilled artisan would have been motivated to use an inducible promoter system such as Hofmann's. In fact, use of these systems in the Laube methods would have rendered those methods unsatisfactory for their intended purpose.

It is thus absolutely unsupportable for the Office to assert that it was obvious to have modified Laube using Mohammadi and/or Hofmann in order to arrive at applicant's recited invention. This is because it is well established that if a proposed modification would render the prior art being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

For these reasons, then, the rejection of claims 1 and 5 under 35 U.S.C. §103(a) is improper. The Office's proposed modification necessitates that the clear teaching of the primary reference as well as the common understanding in the art be ignored and that the modification render it unsatisfactory for its intended purpose. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

CONCLUSION

Applicant respectfully submits that the claims define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated. The examiner is requested to contact the undersigned at (510) 742-9700, ext. 209, should there be any remaining issues that can be dealt with over telephone.

Respectfully submitted,

Date: 11 January 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 5 and 6 have been amended as follows.

5. (Amended) A method according to claim 1, wherein the construct is delivered *ex vivo* into cells taken from a subject [and the cells are reintroduced into the subject].

6. (Amended) A method according to claim [1] 6, wherein the subject is a human.